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Original Article

Oncologic Outcomes of Total Pelvic Exenteration in Locally Advanced Rectal Cancer Without Neoadjuvant Treatment: A Retrospective Cohort Study

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Abstract

Background: The retrospective analysis in total pelvic exenteration (TPE) in locally advanced rectal cancer to find the clinicopathologic variables in preoperative (age, gender, tumor size, site, tumor stage, lymph node involvement) and intraoperative (operative time, blood loss) that can be used to predict long-term survival in patients receiving total pelvic exenteration for advanced primary rectal cancer without neoadjuvant therapy.

Methods: 104 individual medical records with curative total pelvic exenteration for locally advanced rectal cancer had they are reviewed. On long-term survival, the effects of several clinical factors were examined.

Results: The five-year survival rate after total pelvic exenteration was 62.5 percent. The five-year survival rate was 88.9% in Stage II and 57.0% in Stage III, with zero 30 days mortality rate. Univariate analysis showed that postoperative survival was affected by tumor stage, lymphovascular invasion (LVI), intraoperative blood loss, operative time, postoperative complication, occur local recurrence, and occur distant metastasis.

Conclusion: TPE can offer long-term survival and effective local control for patients with clinical T4 or locally advanced rectal cancer.

Keywords: Rectal cancer, Pelvic exenteration, 5 years survival, Local recurrence, Non-neoadjuvant

Introduction

Colorectal cancer is the world's third most prevalent cancer diagnosis and the fourth major cause of cancer-related death. One-third of the tumors occurred in the rectum.[1] Locally advanced rectal cancer (LARC), including T3 and T4 cancers and malignancies involving locoregional lymph nodes, has traditionally been difficult to treat. Surgical excision has been difficult and morbid because of the limitations of the bony pelvis near the anal sphincter and the requirement to maintain autonomic nerves. Following neoadjuvant long-course chemoradiotherapy (LCRT) or short-course hypofractionated radiation (SCRT), total mesorectal excision (TME) is the widely accepted guideline of care for LARC. But some guideline has a variant in indication, such as predicted circumferential margin ≤ 1 mm (CRM), advanced T3 substages (T3c/T3d), and extramural vascular invasion (EMVI), which define the probability of both local recurrence and/or synchronous and future metastatic illness.[2,3]

But the resources in radiotherapy were limited in Thailand, and the delay in treatment led to worst oncologic outcomes later. Achieving a clear margin in rectum cancer is difficult due to its close relation to or growth

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in adjacent organs. Total pelvic exenteration (TPE), an exenterative procedure for these advanced cancers, entails the rectum, bladder, and internal genital organs being removed simultaneously. This study aims to demonstrate the result in patients undergoing complex operative procedures. Prognostic factors for local control or survival were evaluated, along with mortality, local recurrence, disease-free survival, and overall survival rates.

Methods

Cohort Study in the medical record of patients from 2012-2017 AD. This included the middle and lower third of rectal cancer patients diagnosed with stage II or III preoperatively and underwent total pelvic exenteration at …… hospital. The inclusion criteria were 1 diagnosis of middle rectal cancer, 2 denied to radiotherapy after consent. The exclusion criteria were 1 patient unable to have surgery, 2 patients did not accomplish follow-up after surgery, 3 patients had a previous surgery due to an emergency condition of rectal cancer such as obstruction, and 4 patients denied to received adjuvant treatment after surgery. The following information was retrieved for analysis: patient characteristics, cancer information, surgery information, resection margin status, postoperative problems, and length of hospital stay. All patients underwent preoperative staging with colonoscopy and CT chest with the whole abdomen, but some patients underwent pelvic MRI in suspicious T4 from the CT scan. This study's ethics approval was given by the Ethical broad committee ….. hospital. The definition of exenterations was classified as either partial or total, as previously reported.[4] The margin of resection was classified into three categories: macroscopically involved (R2), microscopically involved (R1), and microscopically devoid of malignant cells (R0). The work has been reported in line with the STROCSS criteria.[5]

Statistical Analyses

The statistical program SPSS version 20.0 was used for all statistical analyses. For categorical data, descriptive statistics included frequency and percentage; for continuously distributed variables, mean and standard deviation; or median and range in other cases. If applicable, patient characteristics were compared between two groups using the Chi-square test for categorical data and the Mann-Whitney U test for continuous variables. A Cox proportional hazard model with repeated measures was used to estimate cohort survival. Kaplan-Meier survival curves were produced to retrospectively showed survival outcomes, and significance was shown using a log-rank test to assess the overall survival risk. P 0.05 was regarded as statistically significant for all tests.

Results

A total of 123 cases excluded 10 patients from loss follow-up, 7 patients underwent ostomy procedure before TPE due to obstruction, and 2 patients denied adjuvant treatment. The average age in the remaining 104 cases was 56.96 ± 6.74 years (min-max, 40 - 66 years). Patients' sex was predominantly male in 62 patients (59.6%). The common clinical presentations were bleeding per rectum in 27 (26%), pelvic pain in 26 (25%), and asymptomatic in 20 (19.2%). The patient's demographic showed in Table 1. The organ to be invaded by tumor was the prostate in 41 (39.4%), bladder in 32 (30.8%), vagina and bladder in 11 (10.6%), uterus and bladder in 10 (9.6%), anterior organ to rectum with sacral bone in 8 (7.7), and combined

Table 1 Patient's demographic data

Variable (patients' characteristics)	No. of Patients
Sex (%)	Number (%)
Male : female	62 : 42 (59.6 : 40.4)
Clinical presentation (%)	
Bleeding per rectum	27 (26)
Pelvic pain	26 (25)
Asymptomatic	20 (19.2)
Colonic obstruction	11 (10.6)
Pelvic abscess	7 (6.7)
Fecaluria	7 (6.7)
Urinary tract infection (UTI)	6 (5.8)
Underlying disease (%)	
Cardiovascular disease	34 (32.7)
Diabetes mellitus	15 (14.4)
Rheumatoid arthritis	1 (1)
Chronic kidney disease	1 (1)
Tumor location (%)	
Middle third of rectum	72 (69.2)
Lower third of rectum	19 (18.3)
Anal canal	13 (12.5)
Operation (%)	
Total pelvic exenteration	85 (81.7)
Total pelvic exenteration with sacrectomy and lateral pelvic node dissection	19 (18.3)

of vagina-uterus and bladder in 2 (1.9%). The average preoperative CEA level was 46.66 ± 53.05 ng/ml (min-max, 1.40 - 454.0).

All patients underwent total pelvic exenteration, an average operative time was 343.55 ± 83.49 minutes (min-max, 200-600), and an average blood loss was 712.98 ± 426.14 milliliters (ml) (min-max, 200-2,500). The postoperative complications showed pneumonia in 17 (16.3), wound infection in 13 (12.5), and deep vein thrombosis (DVT) in 3 (2.5) but no mortality in this study. The pathological result was negative circumferential margin (CRM) and R0 in all patients, and the cell differentiation was well and moderate. More pathology information is in Table 2.

Table 2 Pathological result

Variables	
Circumferential margin (mm) (mean ± SD)	4.62 ± 2.66
Distal rectal margin (cm) (mean ± SD)	4.70 ± 2.82
Number harvested lymph node (mean ± SD)	23.48 ± 9.69
Number positive lymph node (mean ± SD)	5.66 ± 4.26
Positive lymphovascular invasion (%)	38 (36.5)
Pathological stage (%)	
II	18 (17.3)
III	86 (82.7)

Abbreviation: millimeters-mm, centimeters-cm

An Oncologic result. According to the stage of disease, the 5 years of survival in Stage II-88.9% and Stage III 57.0%. Figure 1 showed 5 years survival rate among stages. Table 3 showed univariate analysis factors associated with 5 years survival rate. The 3 years survival rate in stage II was 88.9%, and in stage III, is was 79.1%. The local recurrence in stage II was 5.6%, and stage III was 20.9%. The average time to local recurrence is 38.10 ± 38.93 months (min-max, 16-180), and the median time to recurrence is 26 months. Univariates analysis factors associated with local recurrence are in Table 4. The metastasis rate in stage II is 22.2%, and in stage III is 52.3%. The site of metastasis shows in Table 5. The average time to metastasis is 34.59 ± 12.88 months (min-max, 18-64), and the median time to metastasis is 30 months. All patients underwent adjuvant chemoradiation therapy according to their stage of disease.

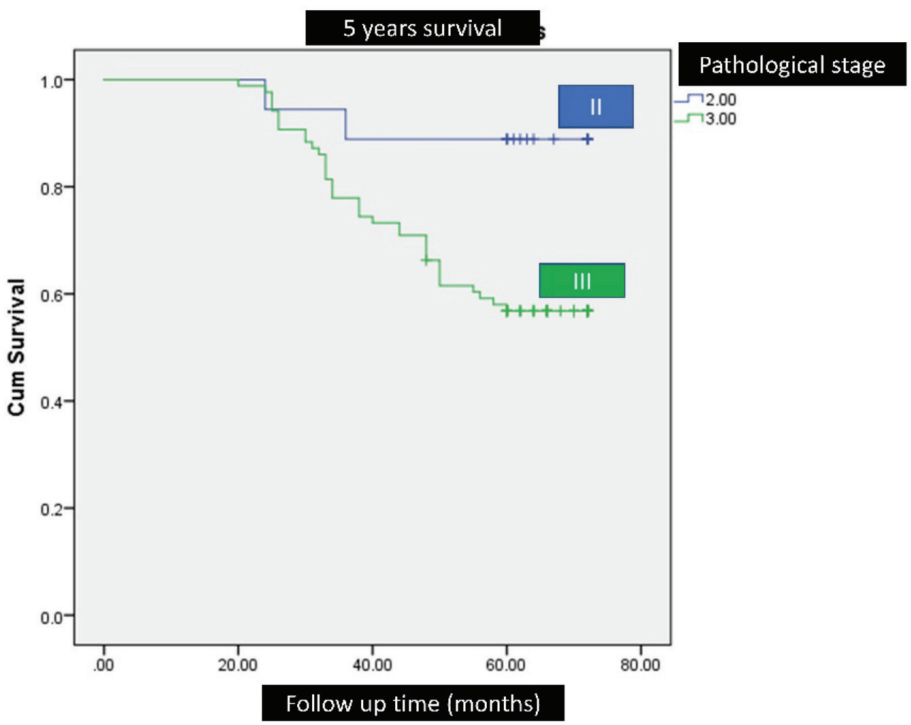

Figure 1 5 years survival among stages of the disease

Table 3 Factors associated to 5 years survival rate

Factor	5 years survival rate		*p*-value
	No	Yes	
Pathological stage (%)			0.014
II	2 (11.1)	16 (88.9)	
III	37 (43)	49 (57)	
LVI positive	27 (71.1)	11 (28.9)	< 0.001
Harvested lymph node	21.79 ± 11.17	24.49 ± 8.61	0.171
Number of positive lymph node	6.10 ± 3.66	5.43 ± 4.60	0.44
Intraoperative blood loss (ml) (mean ± SD)	1,131 ± 567.94	619.41 ± 324.13	< 0.001
Operative time	401.05 ± 102.24	330.70 ± 73.42	< 0.001
Postoperative complication	26 (78.8)	7 (21.2)	< 0.001
Occur local recurrence (%)	15 (78.9)	4 (21.1)	< 0.001
Occur distance metastasis (%)	39 (79.6)	10 (20.4)	< 0.001

Table 4 Factors associated to local recurrence

Factor	Local recurrence		*p*-value
	No	Yes	
Sex			0.037
Male (%)	55 (88.7)	7 (11.3)	
Female (%)	30 (71.4)	12 (28.6)	
Intraoperative blood loss (ml) (mean ± SD)	619.41 ± 324.13	1131 ± 567.94	< 0.001
Operative time	330.70 ± 73.42	401.05 ± 102.24	< 0.001

Table 5 Metastasis site according to the stage of disease

Metastases site	Stage II (%)	Stage III (%)
Liver	-	4 (8.69)
Lung	-	13 (28.26)
Lung & liver	2 (50)	19 (41.30)
Bone	-	1 (2.17)
Brain	1 (25)	3 (6.52)
Carcinomatosis	1 (25)	6 (13.04)

Discussion

Rectal cancer that invasion nearby pelvic organs (especially the urinary bladder) locally, but no distant metastasis could be managed with the aggressive surgical procedure known as pelvic exenteration. It includes a range of operations such as pelvic organ resections, urine diversion, bowel or diversions. This radical procedure induces a significant modification of the quality of life. Previous studies reported 5 years survival rate of 40-52%[6-9] in all locally advanced rectal cancer. The majority of publications that have been published have emphasized survival and complication rates with various treatment approaches.

A margin negative (R0) resection is the main element influencing enhanced survival. It could be technically difficult to obtain negative margins when there is an advanced malignancy with a big volume tumor in the restricted pelvic region and concomitant anatomical deformity. Differentiating between tumor invasions, radiation-induced fibrosis, or local inflammation during intraoperative in these circumstances is one of the most challenging tasks.[10]

Previous studies showed that patients who underwent curative resection with R0 had 5 -a year survival rate of 75%, while no patient with R1 or R2 resection survived for more than two years.[11] In this study, all of the patients achieve R0 resection. Nowadays, the CRM

is a factor of margin resection that is significant in the prognosis of recurrence / metastasis / survival one in refer to margin resection. The study shows it is significantly associated with recurrence and metastasis at a hazard rate (HR) of 6.3 and 2.9 in positive, respectively.HR 2.0 and 1.7 in negative CRM.[12] Recent meta-analysis study show the significance of CRM in oncologic result in positive CRM showed an odd ratio (OR) of 3 years, 5 years local recurrence of 4.35, 4.67, respectively, and OR of 5 years survival is 3.21.[13] Most of the studies recommend CRM at least 1 mm.[14-16] However to keep more CRM negative is likely to advantage to survival; multivariate analysis revealed a 32.4% increase in cancer-specific mortality in the group (> 1 and 5 mm) when compared to another group (> 5 and 10 mm).[17] The main advantage of PE is the much-increased likelihood of resecting the tumor package without exposing malignant cells to the dissection plane.[7]

Regarding the local recurrence rate, this study exhibited a stage III or node-positive rate of 20,9%, which was marginally higher than the 16% in the prior study.[18] Additionally, the study's findings indicate that radiotherapy is an effective local treatment for patients with rectal cancer. A significant finding of research comparing neoadjuvant therapy for rectal cancer to surgery first was a decrease in local recurrence from 8.2% to 2.4%.[19] Insist on the benefit of neoadjuvant treatment, citing a multicenter study that showed a drop in the local recurrence rate from 11% to 5%.[20] This study showed that male, intraoperative blood loss and operative time were associated with local recurrence. The possible explanation is that the male pelvis's anatomy was deep and narrow, leading to difficult assessment and dissection, especially in locally advanced rectal cancer.

About the postoperative complication that affects oncologic outcomes. This study had the common were pneumonia, wound infection, and DVT. The previous study showed that intraabdominal abscess, sepsis, bleeding, and urine leak from ureter anastomosis were common after TPE.[21] Most hypotheses link local recurrence or distant metastasis of cancer to patients' worse survival rates when they have complications. First, exfoliated tumor tissue is implanted in the pelvis, increasing the likelihood of a local recurrence.[22] Second, in terms of infectious consequences such as intra-abdominal abscess, abdominal infection, and pneumonia, the lower survival rates seen in our study and earlier study may be due to immune suppression that causes cancer recurrence and lower survival rates.[23,24] Infections following surgery trigger cytokine cascades that are pro-inflammatory. Tumor necrosis factor-alpha (TNF-), interleukins 1, 6, and 8, natural killer cells, cytotoxic T lymphocytes, and antigen-presenting cells are examples of inflammatory cytokines that may impair their functionality[25-27] and infectious complication following surgery cause delay in the start of adjuvant treatment, which could reduce survival even more.[28,29]

Regarding LVI's positive status. This study shows in a similar way to previous studies. For example, the study in stage II and III colorectal cancer with positive LVI has 5 years of survival at 73% and worsens in positive LVI and perineural invasion(PNI) at 56%.[30] Another study in colorectal cancer showed 5 years survival rate of LVI + patients were significantly lower ($p < 0.001$) compared with that of LVI-negative tumors, resulting as being 44.9% (SE 3.0; median survival 44 months) vs. 64.1% (SE 1.2; median survival 104 months).[31] LVI is now widely recognized as a strong unfavorable prognostic factor and is classified by NCCN recommendations as one of the high-risk features for colon and rectal cancer, alongside positive margins, intestinal obstruction, 12 lymph nodes investigated, perineural invasion, localized perforation, and poorly differentiated histology.

After neoadjuvant was accepted worldwide in locally advanced rectal cancer, the previous study showed a 5 years survival of 56.8% in stage II and 42.3% in stage III,[32] similar to a recent study that showed no difference in overall 5 years survival in comparison between neoadjuvant and adjuvant therapy,[33] but the local recurrence rate is 11.4%.[32] The role of neoadjuvant therapy was improved local control.[34,35]

The study's limitation was the failure to gather some pathological features, such as perineural invasion (PNI) and tumor budding, due to a lack of historical control in the pathology report. The second was selection bias on the decision to TPE was based on an imaging study, CT or MRI, or both. The study of 71 patients showed that 50% of patients diagnosed with T4 rectal cancer who underwent entire TPE had T3 tumors and in another study. who reported that only 61% of 46 patients who underwent TPE for suspicion of bladder involvement had a definitive invasion.[9,36] Finally, the complication was not classified using the Clavien-Dindo system for universal significance.

Conclusion

From our study, TPE can be performed with low morbidity and no perioperative mortality. With a precise and wide margin of surgical dissection, we can achieve a comparable outcome to the previous study,[37,38] especially in the early stages of cancer.

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